Appl. No. 09/592,436

REMARKS / ARGUMENTS

Reconsideration is respectfully requested of the objection to the claims in view of the Whitehouse et al. reference. In particular, the claims were rejected as being anticipated by Whitehouse et al. Applicant respectfully traverses this rejection.

Claims 1 and 14 have been amended to clearly set forth that the method and apparatus of this invention rely on a mass of precursor ions be selected prior to entering the collision cell. Therefore the mass-selective specificity of the first fragmentation step is more mass selective since only ions of one m/z value are injected in the collision cell, and are subsequently fragmented by collision with the gas molecules in the cell.

Whitehouse et al., does not teach nor suggest such a mass selection prior to the collision cell. In particular, Whitehouse et al. provides for mass selection within the collision cell. Therefore ions other than the parent or precursor ions may contribute to the fragmentation products and appear in the background spectra.

Furthermore, Whitehouse et al. does not disclose the permitting of all ions entering the collision cell (which in applicants invention is of only one m/z value) to fragment and produce fragment ions, so that the mass spectrum contains only the fragment ions. In Whitehouse et al., the first fragmentation step is undertaken by admitting all ions into the collision cell without any mass selection. The collision-induced fragmentation that follows in Whitehouse et al. is then done for a specific m/z value. This is described by choosing the resonance frequency (RF and AC field) associated with those ions, for resonance excitation CID fragmentation, while all other ions within the collision cell

are—ideally—unaffected, i.e., they do not resonant excite. Therefore, the mass spectrum will contain all ions in addition to the fragment ions (see column 14, lines 50–54 of Whitehouse et al.).

Accordingly, Whitehouse et al. does not teach nor suggest the claimed method and apparatus of the present invention, in as much as Whitehouse et al. does not teach a method and apparatus that provides a stream of precursor ions from the substance; supplies the stream of precursor ions and a collision gas to a multipole and providing an RF signal to the multipole, whereby the multipole functions as a collision cell; fragments said precursor ions in the RF multipole by collisions with the gas molecules, in order to form primary fragment ions; supplies additional alternating current to the multipole at a frequency selected to cause resonance excitation of a desired primary fragment ion mass-to-charge ratio, whereby ions with said desired primary fragment ion mass-to-charge ratio are excited and undergo collisions with the gas molecules causing production of secondary fragment ions; modulates the alternating current signal applied whereby periods in which said alternating current signal is applied alternate with periods in which the alternating signal is not applied; detects the ion signal after fragmentation with a mass spectrometer and collecting one set of data for one spectrum, representative of the ion spectrum when the alternating current signal is applied and another set of data for another spectrum, representative of the ion spectrum when the alternating current signal is not applied; whereby said other spectrum can be subtracted from said one spectrum, to generate a subtracted spectrum showing the secondary fragment ions without the presence of the primary fragment ions except for any said primary fragment ions which are generated.

Moreover, applicant notes that the ion guide as described in Whitehouse et al. is an ion storage device (see, for example, column 8, lines 31–32), and not specifically a flow-through mass analyzer for selecting parent ions as in the current invention. In particular,

the mass selection and fragmentation steps are performed in the same multipole ion guide in Whitehouse (se , for example, column 8, line 36, to column 9, line 18). As previously mentioned, this can be contrasted to the present invention where mass selection occurs separate from the fragmentation multipole ion guide. Since Whitehouse et al. is not concerned with the same proximate problem as the invention there can be no prima facie case of obviousness of modifying Whitehouse et al. to provide the invention. In this regard see *In re Pye,* 148 USPQ 426, 429 (CCPA 1966) wherein the court held:

> "While, as an abstract proposition, it might be possible to select certain statements from Fikentscher a mechanically combined and with Touey to arrive at appellants' claimed combination, we find absolutely no basis for making such a combination. Neither reference is directed to the problem solved by appellants' invention, namely developing a cleaning composition for the skin having improved lubricity characteristics. In our view only appellants' specification suggests any reason for combining the teachings of the prior art but use of such suggestion is, of course, improper under the mandate of 35 U.S.C. 103. *In re Schaffer,* 43 CCPA 758, 229 F.2d 476, 108 USPQ 326." (emphasis added).

Applicant submits that there is no motivation to modify Whitehouse et al. to provide the invention. Whitehouse et al. nowhere recognizes the advantages of mass selection prior to the collision cell according to the invention. Without a suggestion of these advantages Whitehouse et al. cannot be obviously modified.

See *In re Gordon,* 221 USPQ 1125, 1127 (Federal Circuit 1984):

> "We are persuaded that the board erred in its conclusion of prima facie obviousness...The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."

In applicants submission there is not even the most remote suggestion in any way, shape or form of modifying the Whitehouse et al. method or apparatus for the purposes of the present invention as described and now claimed.

Accordingly, it is respectfully submitted that all of the rejections have been addressed, and that the present application is in condition for allowance and an early notice to that effect is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Should the Examiner have any further issues outstanding, applicant invites the Examiner to call the undersigned at (416) 957-1697.

Respectfully submitted,
Bereskin & Parr

By _____
Stephen M. Beney
Registration No. 41,563
(416) 957-1697

Appl. No. 09/592,436

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 1 has been amended as follows:

1. (Twice Amended)A method of analyzing a substance, the method comprising:

(1) providing ~~creating a~~ stream of precursor ions from ~~in~~ said substance;

(2) supplying the stream of precursor ions and a collision gas to a multipole and providing an RF signal to the multipole, whereby the multipole functions as a collision cell;

(3) fragmenting said precursor ions in the RF multipole by collisions with the gas molecules, in order to form primary fragment ions;

(4) supplying additional alternating current to the multipole at a frequency selected to cause resonance excitation of a desired primary fragment ion mass-to-charge ratio, whereby ions with said desired primary fragment ion mass-to-charge ratio are excited and undergo collisions with the gas molecules causing production of secondary fragment ions;

(5) modulating the alternating current signal applied in step (4) whereby periods in which said alternating current signal is applied alternate with periods in which the alternating signal is not applied;

(6) detecting the ion signal after fragmentation with a mass spectrometer and collecting one set of data for one spectrum, representative of the ion spectrum when the alternating current signal is applied and another set of data for another spectrum, representative of the ion spectrum when the alternating current signal is not applied;

whereby said other spectrum can be subtracted from said one spectrum, to g nerate a subtracted spectrum showing the s condary fragment ions without the presence of the primary fragment ions except for any said primary fragment ions which are generated by step (4).

Claim 14 has been amended as follows:

14 (Twice Amended) An apparatus, for analyzing a substance by resonance excitation of selected ions and selective collision-induced dissociation, the apparatus comprising:

an ion source for generating a stream of precursor ions;

a collision cell, including a quadrupole rod set, for receiving the ~~a~~ stream of precursor ions and provided with a collision gas, for collision-induced dissociation between the precursor ~~parent~~ ions and the buffer gas;

a power supply connected to the quadrupole rod set for generating an RF field in the quadrupole rod set for guiding fragment ions produced by the collision-induced dissociation between the ions and the buffer gas and for applying an additional alternating current field at a frequency selected to excite a desired ion;

a modulation means connected to the power supply, for modulating the alternating current signal, whereby periods in which said alternating current signal are applied alternate with periods in which the alternating current signal is not applied.

Claim 17 has been amended as follows:

17. (Amended) An apparatus as claimed in claim 15, which includes a first mass analysis section for selecting a precursor ~~parent~~ ion.